

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 July 1999 (06.07.99)	
International application No. PCT/US98/25253	Applicant's or agent's file reference PCT 180/95
International filing date (day/month/year) 25 November 1998 (25.11.98)	Priority date (day/month/year) 28 November 1997 (28.11.97)
Applicant TEDDER, Thomas, F.	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

09 June 1999 (09.06.99)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

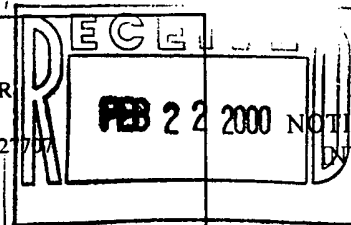
<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer C. Carrié</p> <p>Telephone No.: (41-22) 338.83.38</p>
--	---

PATENT COOPERATION TREATY

09/555349

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

COPY

To: RICHARD E. JENKINS
JENKINS & WILSON, P.A.
SUITE 1400 UNIVERSITY TOWER
3100 TOWER BOULEVARD
DURHAM, NORTH CAROLINA 27707

PCT

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing
(day/month/year)

18 FEB 2000

Applicant's or agent's file reference
180/95 PCT

IMPORTANT NOTIFICATION

International application No.

PCT/US98/25253

International filing date (day/month/year)

25 NOVEMBER 1998

Priority Date (day/month/year)

28 NOVEMBER 1997

Applicant

DUKE UNIVERSITY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

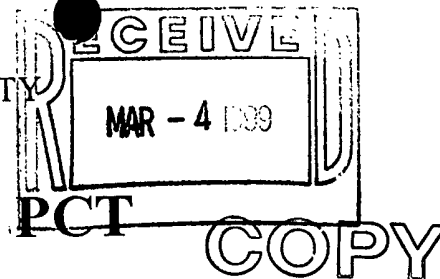
Facsimile No. (703) 305-3230

Authorized officer

CARRIE MARLENE STROUP

Telephone No. (703) 308-0196

PATENT COOPERATION TREATY



From the INTERNATIONAL SEARCHING AUTHORITY

To: RICHARD E. JENKINS
JENKINS & WILSON, P.A.
SUITE 1400 UNIVERSITY TOWER
3100 TOWER BOULEVARD
DURHAM, NORTH CAROLINA 27707

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference PCT 180/95	Date of Mailing (day/month/year) 02 MAR 1999
International application No. PCT/US98/25253	International filing date (day/month/year) 25 NOVEMBER 1998
Applicant DUKE UNIVERSITY	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

C. Stroup

Telephone No. (703) 308-0196

Handwritten: docketed
4/2/99
5/2/99

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 180/95 PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/25253	International filing date (day/month/year) 25 NOVEMBER 1998	Priority date (day/month/year) 28 NOVEMBER 1997
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant DUKE UNIVERSITY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 09 JUNE 1999	Date of completion of this report 02 FEBRUARY 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer <i>Carrie Marlene Stroup</i> CARRIE MARLENE STROUP
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/25253

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments):*

☒ the international application as originally filed.

☒ the description, pages 1-81, as originally filed.

pages NONE, filed with the demand.

pages NONE, filed with the letter of _____.

pages _____, filed with the letter of _____.

☒ the claims, Nos. 1-28, as originally filed.

Nos. NONE, as amended under Article 19.

Nos. NONE, filed with the demand.

Nos. NONE, filed with the letter of _____.

Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1/5-5/5, as originally filed.

sheets/fig NONE, filed with the demand.

sheets/fig NONE, filed with the letter of _____.

sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☒ the description, pages None.

☒ the claims, Nos. None.

☒ the drawings, sheets/fig None.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/25253

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)	Claims <u>1-81</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-81</u>	NO
Industrial Applicability (IA)	Claims <u>1-81</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-81 lack an inventive step under PCT Article 33(3) as being obvious over Sato et al (1996) in view of Knight (US Patent 5,675,063). Sato et al teach transgenic mice overexpressing CD19, which resulted in a phenotype of the production of autoantibodies, a heightened responsiveness to weak antigens, and the production of anti-ssDNA antibodies of the IgG isotype (pg 4377, col 1, para 2). Knight et al teach the use of hybridomas for the production of monoclonal antibodies and kits containing such. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to produce hybridomas by fusing antibodies derived from transgenic mice overexpressing CD19 with an immortalizing cell for the purpose of producing a monoclonal antibody with a high affinity for a weak or self antigen. One would be motivated to do this to utilize said antigens for identifying self antigens.

Claims 1-81 meet the criteria set out under PCT Articles 33(2) and 33(4).

----- NEW CITATIONS -----

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/25253

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(6): A61K 39/395, 49/00, 63/00; G01N 33/53 and US Cl.: 424/9.1, 93.1, 93.21, 130.1, 141.1, 178.1; 435/7.1

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where Applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

09/555349

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PCT 180/95	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US98/25253	International filing date (day/month/year) 25 NOVEMBER 1998	(Earliest) Priority Date (day/month/year) 28 NOVEMBER 1997
Applicant DUKE UNIVERSITY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (See Box I).
2. ☐ Unity of invention is lacking (See Box II).
3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
 - ☐ filed with the international application.
 - ☐ furnished by the applicant separately from the international application,
 - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - ☐ transcribed by this Authority.
4. With regard to the title,
 - ☒ the text is approved as submitted by the applicant.
 - ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - ☒ the text is approved as submitted by the applicant.
 - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
 - Figure No. _____ ☐ as suggested by the applicant.
 - ☐ because the applicant failed to suggest a figure.
 - ☐ because this figure better characterizes the invention.
 - ☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/25253

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 39/395, 49/00; G01N 33/53

US CL :424/9.1, 93.1, 93.21, 130.1, 141.1, 178.1; 435/7.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/9.1, 93.1, 93.21, 130.1, 141.1, 178.1; 435/7.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,675,063 A (KNIGHT et al) 07 October 1997, see Abstract.	1,8
Y	BURNETT et al. Human Monoclonal Antibodies to Defined Antigens. Human Hybridomas and Mab (1985) Plenum Press. pp113-133, see pages 113-114.	19-25
X	BOHLEN et al. Cytolysis of Leukemic B-Cells by T-Cells Activated via Two Bispecific Antibodies. Cancer Research. 15 September 1993, Vol. 53, pages 4310-4314, see Abstract.	1-18

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

10 FEBRUARY 1999

Date of mailing of the international search report

02 MAR 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

C. Stroup

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/25253

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SATO et al. CD19 Regulates B lymphocyte Signaling Thresholds Critical for the Development of B-1 Lineage Cells and Autoimmunity. J Immunology. 1996, Vol. 157, pages 4371-4378, see entire document.	1-28
X	ZHOU et al. Tissue-Specific Expression of the Human CD19 Gene in Transgenic Mice Inhibits Antigen-Independent B-lymphocytes Development. Molecular and Cellular Biology. June 1994, Vol. 14, No. 6, pages 3884-3894, see Abstract.	1-18, 25-26
Y	BRINK et al. Immunoglobulin M and D Antigen Receptors are Both Capable of Mediating B Lymphocyte Activation, Deletion, or Anergy After Interaction with Specific Antigen. J. Exp. Med. October 1992, Vol. 176, pages 991-1005, see Abstract.	1-18, 25-26

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/25253

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

DATABASES: MEDLINE, WPIDS, BIOSIS, APS

SEARCH TERMS: MONOCLONAL ANTIBODY, TRANSGENIC MICE, PERIPHERAL TOLERANCE,
OVEREXPRESSION/UPREGULATED CD19, HYBRIDOMAS, DIAGNOSTIC KIT, DOUBLE TRANSGENIC, and
AUTOIMMUNITY.

INTERNATIONAL SEARCH REPORT

Inter val Application No
PCT/GB 95/02586

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N5/16 C07K16/00 A61K48/00 A61K49/00 G01N33/50
A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K G01N A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 23760 (THE UNITED STATES OF AMERICA) 27 October 1994 *see the whole patent* ---	1-5,8, 11,19-25
X	PLANT PHYSIOLOGY, vol. 102, 1993 pages 287-293, CHENGBIN XIANG ET AL. 'The anti-nptII gene' *see the whole article* ---	1-4,8, 11,12, 15,19, 21,22
X	INTERNATIONAL IMMUNOLOGY, vol. 5, no. 8, 1993 pages 975-984, E. DZIERZAK ET AL. 'Thy-1 tk transgenic mice with a conditional lymphocyte deficiency' *see the whole article* ---	1-5,8, 10, 19-22,26
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search

29 February 1996

Date of mailing of the international search report

15.03.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Marie, A

INTERNATIONAL SEARCH REPORT

Inter vnaI Application No
PCT/GB 95/02586

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DIFFERENTIATION, vol. 55, 1993 pages 27-35, M.J. GARCIA-IGLESIAS ET AL. 'Specific expression in adult mice and post implantation embryos of a transgene carrying the histon H1 regulatory region' *see the whole article* ---</p>	8
X	<p>MUSCLE AND NERVE, vol. 17, 1994 pages 975-980, I. KINOSHITA ET AL. 'Utilization of myoblasts from transgenic mice to evaluate the efficacy of myoblast transplantation' *see the whole article* ---</p>	8
X	<p>BRAIN PATHOLOGY, vol. 4, 1994 pages 3-20, A. AGUZZI ET AL. 'Transgenic and knock-out mice: models of neurological disease.' *see the whole article* ---</p>	1-5,7-9, 11,16, 19-23
X	<p>WO,A,91 15116 (AMRAD CORPORATION LIMITED) 17 October 1991 *see the whole patent* -----</p>	1-7,11, 12,15, 16,24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 95/02586

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9423760	27-10-94	AU-B- 6586494	08-11-94
WO-A-9115116	17-10-91	NONE	